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AN EXPERIMENTAL ANALYSIS OF MECHANISMS ENGAGED IN REFLEX INHIBITION OF INTESTINAL MOTILITY

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GÖTEBORG 1959

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FROM THE DEPARTMENT OF PHYSIOLOGY, UNIVERSITY OF GÖTEBORG, AND THE DEPARTMENT OF SURGERY I, SAHLGRENSKA SJUKHUSET, GÖTEBORG, SWEDEN

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CHAPTER I

Introduction

> "On no subject in physiology do we meet with so many discrepancies of fact and opinion as in that of the physiology of the intestinal movements". (BAYLISS and STARLING)

Since the classical study of intestinal motility by BAYLISS and STARLING (1899) it has been generally assumed that the parasympathetic and the sympathetic components of the autonomic nervous system exert a central, reciprocal control over the activity of intestinal smooth muscle. Thus vagal fibres, which constitute the parasympathetic innervation to the small intestine, have an excitatory influence on the motility, while sympathetic fibres running in the splanchnic outflow convey centrally induced inhibitory effects. This innervation principle would allow centrally induced inhibition of intestinal motility to occur in two different ways: by decrease in vagal tone or by increase in sympathetic tone. A decrease or even a complete exclusion of a prevailing vagal activity does not, however, give rise to a complete inhibition, since the intestinal motility is basically a consequence of purely local mechanisms. On the other hand, activation of the splanchnic nerves, directly or reflexly, can give rise to a complete inhibition of all intestinal motility. Exactly how this inhibitory influence is brought about in reflex excitations of the sympatho-adrenal system is, however, not known in detail. At least four essentially different modes of action may *a priori* be considered:

1. An activation of centrally controlled sympathetic nerve fibres whose ramifications make direct contact with the intestinal smooth muscle cells, thus constituting a specific inhibitory innervation.

2. An 'overflow' of the adrenergic transmitter, released at the vasoconstrictor nerve endings to the intestinal blood vessels, inducing an inhibitory action on the adjacent intestinal smooth muscle cells.
3. A shift in the local chemical environment of the intestinal smooth muscle, secondary to the reduction in blood supply brought about by sympathetic vasoconstrictor activity.
4. An increased secretion of catechol amines from the adrenal medulla, induced by splanchnic nerve fibre activation, the hormones reaching the intestinal smooth muscle cells by way of the blood stream.

1. *Inhibition caused by a specific inhibitory innervation of the intestinal smooth muscle cells.*

It is a widely accepted view that this principle of sympathetic inhibitory action on the small intestine, referred to in practically all textbooks of physiology, forms the most important mechanism for induction of reflex inhibition of intestinal motility. Since the work of BAYLISS and STARLING (1899) a great number of studies have been carried out which have been interpreted as evidence for the existence of a direct inhibitory innervation (for ref. see GARRY 1957). This opinion was supported by e. g. v. LEHMAN (1913) who, in experiments on anaesthetized dogs, showed that reflex inhibition of intestinal motility was abolished after complete section of the splanchnic nerves. After extensive studies of the control of intestinal motility, YOUMANS (1949) further stressed the generally accepted view that the main inhibitory influence on the intestinal smooth muscles was exerted by a direct inhibitory adrenergic innervation. On the basis of pharmacological studies of intestinal preparations, treated with botulinum toxin, AMBACHE (1951) suggested that there were two functionally different types of ganglion cells in the myenteric plexus, referring also to KUNTZ' histological investigations (1922). The suggested inhibitory neurons were not only engaged in local reflexes but might also, in some way or other, be linked up with the extrinsic innervation of the gut. Recently GARRY and GILLESPIE (1955), in *in vitro* experiments, presented results which were taken by them as additional evidence of a sympathetic inhibi-

tory innervation of the intestinal smooth muscle cells. — The very concept of such a specific, centrally controlled inhibitory innervation has, however, been questioned by CELANDER in a recent study (1956, 1959). According to him earlier observations, which have hitherto been accepted as evidence of specific inhibitory fibres, may be explained along quite different lines. The main reason why the supposed existence of sympathetic inhibitory fibres to the gut has been so widely accepted is, according to CELANDER, the fact that in practically all previous studies the sympathetic nerve fibres have been stimulated with supraphysiological frequencies. CELANDER presents evidence indicating that an 'overflow' of transmitter substance from the vasoconstrictor nerve endings, together with the decrease of the intestinal blood flow, may be solely responsible for the motor inhibition seen when the splanchnic nerve fibres to the gut are directly stimulated. At physiological frequencies, below ten impulses per second, the amount of adrenergic transmitter released would not be, however, sufficient to induce significant effects on non-innervated cells (CELANDER 1954, BROWN and GILLESPIE 1957, BROWN, DAVIES and GILLESPIE 1958). This circumstance alone would make it desirable to perform a more detailed analysis of the mechanisms responsible for the inhibition of intestinal motility, which occurs whenever the sympatho-adrenal system is reflexly activated. Further, even if specific inhibitory fibres should exist, the other three mechanisms mentioned above may also contribute significantly to the motor inhibition and a quantitative analysis of their relative importance would therefore be of special interest.

2. *Inhibition caused by an 'overflow' of the transmitter released at the vasomotor nerve endings.*

From the classical studies of CANNON and his co-workers (see CANNON and ROSENBLUETH 1937, and ROSENBLUETH 1950) it was known that, at least under certain circumstances, the adrenergic transmitter substance diffuses away from the site of release in such concentrations that it can even induce remote effects via the blood stream on other organs. CANNON and his school therefore arrived at the opinion that the sympathetic transmitter substance was mainly eliminated by way of diffusion to the extracellular fluid

and the blood stream, in contrast to the local enzymatic destruction of acetylcholine at cholinergic nerve endings. In this way the adrenergic transmitter overflow would act in synergism with the hormones from the adrenal medulla. FOLKOW (1952), in a study of the physiological range of discharge rate within the sympathetic nervous system, presented evidence to show that normally the vasoconstrictor fibres hardly exceed an upper discharge rate of about 8 to 10 impulses per second even at extreme excitations of the vasomotor centre, and that the 'resting' tonic activity is around 1 to 2 impulses per second at most. His experimental results also indicated that at physiological discharge rates the adrenergic transmitter is almost completely eliminated at the site of release, possibly by an enzymatic process, and that a significant overflow probably only takes place at supraphysiological discharge rates, as induced by direct high frequency stimulation in animal experiments. These results were extended and confirmed by CELANDER (1954) in a quantitative study of the sympathetic neuro-humoral control of the circulation. They have also been fully confirmed more recently by BROWN and GILLESPIE (1957) and BROWN, DAVIES and GILLESPIE (1958). The transmitter overflow mechanism, then, is less likely normally to be of any importance for the establishment of intestinal inhibition.

3. *Inhibition caused by a decreased intestinal blood flow.*

It is well known that smooth muscle tone is much dependent on the local chemical environment, with regard to its oxygen and carbon dioxide tension, pH etc. As activation of the intestinal vasoconstrictor fibres will certainly decrease the blood supply to the gut, provided that the perfusion pressure is not proportionally raised, increased vasoconstrictor tone will probably lead to a local decrease of oxygen tension and increased carbon dioxide tension. As far back as 1873, VON BASCH suggested that the intestinal inhibition seen on splanchnic stimulation might be a consequence of the decreased blood supply to the gut. Several authors have observed inhibition of intestinal motility when the experimental animals are exposed to anoxia (SCHNOHR 1934, WELTZ and WERZ 1942), but the possibility cannot be excluded that in these experiments other

mechanisms besides the local anoxia were involved. In experiments on isolated smooth muscle preparations, FURCHGOTT and SCHORR (1950) observed that anoxia produced a marked decrease in tone and activity of the preparation. BEAN and SIDKY (1957) studied the effects of low oxygen tension on intestinal blood flow and motility in blood-perfused segments of dog intestine. They found that low oxygen tension of the perfused blood caused not only a marked depression of intestinal motility but also a dilatation of the intestinal blood vessels. They further observed that alterations in intestinal tone and motility, evoked by low oxygen tension, could influence the effect of vasculatory changes *per se*. A more direct approach to the question of the influence of the intestinal blood supply on motility was made by CELANDER (1956, 1959). He correlated the degree of controlled reduction of intestinal blood flow, induced by partial mechanical obstruction of the aorta, with the motility changes in a denervated intestinal loop *in situ*. However, there appears to have been no investigation made which includes a systematic study of the correlation between the degree of blood flow reduction and the consequent change of intestinal motility. At any rate, this mechanism for intestinal motility inhibition has not been quantitatively compared with other factors inhibiting the motility of the gut in one and the same experiment.

4. *Inhibition induced by hormones released from the adrenal medulla.*

It is a well established fact that adrenaline, and also noradrenaline, when administered by the blood stream or released from the adrenal medulla, induce inhibition of intestinal motility. There are, however, practically no reports concerning the *in vivo* correlation between the extent of activation of the medullary cells and the resulting intestinal inhibitory response. It would thus be most interesting to know to what extent intestinal motility *in vivo* is affected by the reflexly induced variations of discharge rate in the fibres to the adrenal medulla and the consequent variations in the blood concentrations of the released catechol amines. In 1912 HOSKINS and MCCLURE had already observed that in dogs 'intestinal depression is caused by injections of epinephrin, decidedly smaller in amount than those requisite to cause increase of blood pressure',

an observation indicating a relatively high sensitivity of the intestine to this hormone. DURANT (1925) was able to confirm these observations in both cats and dogs, where the infused amounts of adrenaline were about 2 μg/kg body weight/minute. This is from the physiological point of view a fairly large amount, however, since even in the intense reflex sympathetic excitation seen in strong asphyxia the adrenal catechol amine secretion in cats does not exceed 2 to 3 μg/kg/minute. In guinea pigs, on the other hand, intestinal motility appears to be affected first by adrenaline concentrations big enough to induce blood pressure rises (JACOBSOHN and KAHLSON 1937). DRAGSTEDT and HUFFMAN (1928) studied the adrenaline effects on intestinal motility in anaesthetized and awake dogs and obtained results similar to those of DURANT in the anaesthetized animals. In the awake animals, however, considerable blood pressure rises could be obtained by adrenaline doses of 0.5 to 1.3 μg/kg/minute, without any effect on intestinal motility. In man, the dose of adrenaline reported to induce inhibition varies somewhat (KATSCH 1913, GANTER 1924, DANIÉLOPOLU, SIMICI and DIMITRIU 1925). WEITZ and VOLLERS (1927) report that an intravenous injection of only 1 μg in total of adrenaline appears to be the smallest amount that has a definite inhibitory effect on intestinal motility in man.

With regard to the question as to the circumstances in which a reflex catechol amine secretion takes place, HEYMANS was able to show in 1929 that an increased secretion occurs e. g. on clamping the carotids or after bleeding. In recent years, the amounts of catechol amines secreted in response to different stimuli and under 'resting' conditions have been directly measured in animal experiments (BRAUNER et al. 1950, KAINDL and EULER 1951, HOLTZ et al. 1952, EULER and FOLKOW 1953, WATTS 1956). Under 'resting' conditions in anaesthetized but otherwise largely intact animals, the secretion from the adrenal medulla appears to be well below 0.1 μg/kg body weight/minute, increasing to 0.2—0.5 μg on carotid occlusion, where noradrenaline, at least in cats, makes up the greater fraction of the hormone release. On e. g. massive afferent stimulation of 'pain fibres' the total catechol amine output in cats, which then appears to be dominated by adrenaline, amounts to up to 0.6—0.7 μg. In severe asphyxia the secretion can sometimes, as mentioned, amount to 2—3 μg/kg/minute (RAPELA and HOUSSAY

1952, EULER and FOLKOW 1953). Since in man, the adrenal glands contain practically only adrenaline, about 85 to 90 per cent of the catechol amine content (WEST, SHEPHERD and HUNTER 1951), it is likely that in this species adrenaline will dominate in the adrenal medullary discharge. CELANDER (1954) has calculated the amount of catechol amines released into the blood stream per stimulation shock from both adrenal glands in cats, when all the medullary cells were activated. On an average it amounts to about 0.008 μg/kg body weight. If all the adrenal cells were activated at ten impulses per second, and if this frequency is looked upon as the very maximum frequency that occurs under physiological conditions, it would mean a secretion of about 5 μg per kg body weight per minute. This 'theoretical' maximum is thus well above the highest values seen even on extreme reflex excitation of the adrenal glands. This indicates that the upper limit of sympathetic discharge is normally below rather than above ten impulses per second, if it is assumed that intense asphyxia leads to excitation of all the adrenal medullary cells.

Considering these amounts of catechol amines secreted under physiological conditions, it would be interesting to see to what extent variations in the activity of the adrenal medulla contribute to reflexly induced changes in intestinal motility. The relatively few studies which have some bearing on this question are either contradictory or they do not allow any definite conclusions to be drawn regarding the role of the adrenal glands as compared with other mechanisms. JACOBSOHN and KAHLSON (1937), working on guinea pigs, and HOLTZ and SCHÜMANN (1949), studying cats, were able only exceptionally to induce inhibition of intestinal motility when the carotid arteries were clamped. BRAUNER et al. (1950), on the other hand, fairly regularly obtained intestinal inhibition by carotid occlusion in cats. Contradictory results have been reported of the effect of acute bleeding on intestinal motility in dogs (VAN LIERE, NORTHUP and STICKNEY 1944, HAMILTON, COLLINS and OPPENHEIMER 1944, WAKIN and MASON 1945, NECHELESS et al. 1946). YOUMANS et al. (1939) induced hypotension by acetylcholin-injections and studied the effects on intestinal motility. The inhibitory responses obtained were ascribed partly to a reflex release of adrenaline from the adrenal medulla, partly to sympathin, released

at reflexly activated adrenergic nerve endings when the blood pressure fell.

In spite of previous extensive studies of the factors involved in intestinal motor inhibition, the experiments have generally not been arranged so as to allow quantitative evaluation of the part played by the different mechanisms mentioned above. It was decided to make an attempt to analyse the interrelationship of the four possible routes over which intestinal inhibition can be elicited:

1) A centrally controlled, specific inhibitory innervation of the intestinal smooth muscle;
2) An 'overflow' of transmitter substance from vasoconstrictor nerve endings;
3) Secondary effects of decreased intestinal blood flow caused by vasoconstrictor activity;
4) A secretion of hormones from the adrenal medulla.

In order to induce reflex excitation of the sympatho-adrenal system the experimental animals were exposed to occlusion of the carotid arteries, graded withdrawal of blood and electrical or mechanical stimulation of thin afferent fibres in somatic nerves. In the course of these procedures for inducing reflex inhibition of intestinal motility, the effects on motility and intestinal blood flow of exclusion of the adrenal medullary secretion and of denervation of the intestinal segment were studied. The reflexly induced effects were also quantitatively compared with the effects obtained by graded electrical stimulation of the splanchnic nerves, with and without the adrenal glands left intact, and also with the inhibitory responses induced by distension of other parts of the intestine. Further, the effects of intravenous infusion of catechol amines, in concentrations corresponding to those obtained on reflex activation of the adrenal medulla, were studied. Lastly, reduction of the intestinal blood supply was mechanically induced and the effect on intestinal motility was observed.

CHAPTER II

Methods

The experiments were performed on anaesthetized cats, varying between 2.1 and 4.4 kg in body weight. During an initial ether anaesthesia a cannula was inserted in the right femoral vein. The animals were then given either nembutal 20 mg per kg body weight, injected slowly intravenously, or chloralose-urethane, 40 and 100 mg per kg respectively. The animals were kept on a heating pad, which was thermostatically regulated so that the body temperature was kept around 37—38° C. A tracheal cannula was inserted and the left femoral artery was connected to a mercury manometer for recording of the arterial blood pressure. The two common carotid arteries and the two vagal nerves were prepared free in the neck; the vagal nerves were cut at the start of the recording of the intestinal motility and blood flow.

The abdomen was opened in the midline, and the colon and the greater part of the small intestine were cautiously extirpated with the exception of 20—25 cm of the proximal jejunum, whose range of blood supply was found to be suitable for the blood flow recorder used. From this part of the jejunum, a segment of 7—10 cm was isolated by dividing the intestine between ligatures. The distal end of this intestinal segment was then opened, its content was removed and a glass tube was inserted which, by way of rubber tubes and an adaptable pressure reservoir, was connected to a piston recorder, after which the system was filled with Tyrode solution. By lowering or raising the reservoir the pressure within this intestinal section could be set at any wanted level, but was generally kept at 10 cm of water. In this way the motility of the jejunal section, which was isolated from the adjacent parts of the gastro-intestinal tract but otherwise left intact *in situ*, could be continuously recorded by measuring its volume changes with the aid of the piston recorder.

Great care was taken not to damage the arterial blood supply, the venous drainage or the innervation of the isolated jejunal part.

In order to record the blood flow through the jejunal section the superior mesenteric vein was cautiously prepared free just where it enters the portal vein and all its branches except those draining the jejunal segment were ligated. The animal was heparinized and an optical drop recorder unit, which had been previously siliconized, was connected to the superior mesenteric vein so that the total venous outflow from the jejunal section had to pass the recorder on its way to the portal vein and the liver. In some cases the outflow from the drop recorder was diverted into one of the femoral veins, since it often proved technically difficult to insert the cannula into the proximal end of the superior mesenteric vein. The drop recorder operated an ordinate writer with which the heights of the ordinates were practically *inversely* proportional to the rate of the blood flow with an error not bigger than about 5 per cent, except at extremely small or big flow volumes. The polyethylene cannula, by way of which the blood was diverted back to the animal from the drop recorder, had a sidetubing through which the outflow from the jejunal segment could be led off and directly measured with a graded test tube. The number of blood drops passing the drop recorder during a given period of time was then counted, while at the same time the blood volume passing out from the drop recorder through the side tube was directly measured. In this way the drop recording could now and then be exactly correlated to the actual blood flow. The pressure drop across the flow recorder unit was quite small, not more than 3—5 cm of water at the blood flow rates occurring in the present experiments, and therefore it did not significantly disturb the haemodynamic characteristics of the vascular bed studied.

When the hormonal component of the sympatho-adrenal system, i. e. the adrenal glands, was to be eliminated the following procedures were used. In some of the experiments both adrenal glands were definitely excluded by extirpation or by ligatures placed around the stem of the glands. In other cases, temporary exclusions of the adrenal secretion were made possible with the aid of the following arrangement: After extirpation of the right adrenal gland a fine polyethylene catheter was introduced into the distal part of the vein draining the intact left adrenal gland, so that the catheter tip was

lying quite close to the gland. A fine thread was loosely placed around the central end of the adrenal vein, just where it enters the renal vein or the inferior caval vein. During reflex excitations of the sympatho-adrenal system the secretion from the remaining left adrenal gland could be temporarily drained off via the catheter by obstructing the central end of the adrenal vein with the ligature. In this way, the effect of sympathetic stimulation on the intestinal motility and blood flow could be studied under circumstances where the hormonal component was excluded, and this component could be added simply by allowing the venous flow from the adrenal gland to reach the inferior caval vein in the normal way. If, during a period of reflex sympathetic activation, the adrenal blood had been drained off and collected, it could be re-injected into the circulation when the animal had returned to the 'resting' state and the effect of the secreted catechol amines on intestinal motility and blood flow could thus be studied selectively.

It was also found desirable to eliminate only the direct nervous influence on the intestine without interfering with the adrenal glands. This was performed by cutting all the nerves running along the superior mesenteric artery to the intestinal segment studied. In addition the artery was surrounded with a piece of cotton soaked in xylocaine in order to block any direct nervous connection to the intestine which might possibly remain. In this way, motility and blood flow in the intestinal segment could be studied during periods of reflex symphathetic activation with all direct nervous connections eliminated, but with the hormonal component of the sympatho-adrenal system entirely intact.

In order to induce reflex excitations of the sympatho-adrenal system, the following procedures were used:

1) Occlusion of the common carotids. Since both vagal nerves had been cut at the beginning of the experiments and the aortic baroreceptors were thus denervated, the carotid occlusion induced a pronounced reflex sympathetic activation by the combined effect of the unloading of the carotid baroreceptors and the reduced blood supply to the chemoreceptors.
2) Graded withdrawal of blood. A cannula was inserted into one of the femoral arteries and blood could be drained from the animal in any wanted amount, and re-infused later on if desired.

3) Stimulation of 'pain fibres' from the limbs. It is well known that activation of pain fibres can elicit pronounced reflex excitation of the sympatho-adrenal system (see e. g. v. EULER and FOLKOW 1953). Since the majority of the pain fibres belong to the C fibre group, they will only be activated by relatively strong excitation. A bipolar silver electrode and a Grass stimulator, Model 4 B, were used. The frequency was varied between 10 to 80 impulses per second and the voltage was usually increased up to 5—15 volts. A more selective stimulation of the afferent C fibre group can be obtained by heating a mixed nerve up to around 45 degrees C or by mechanical stimulations (see C. v. EULER 1947). Therefore either one of the nerve trunks in the brachial plexus or the saphenous nerve of the hind limb was prepared free and divided so that the central end could be stimulated in this way. Evidence of an excitation of the thin afferent nociceptive fibres was easily obtained by studying the reflex effects on the respiration, the somato-motor reflexes, the blood pressure and also by observing e. g. the effects on the pupil.

Since it was of great interest to compare the effects of reflex excitations of the sympatho-adrenal system on intestinal motility and blood flow with the effects that could be induced by graded, electrical stimulations of the splanchnic nerves, the following preparations were made. It is technically quite difficult to prepare free for direct stimulation the great and the small splanchnic nerves on both sides, because the nerves on the right side pass under the liver and the big vessels. This was therefore performed in a few experiments only, in order to see whether the effects of stimulation differed significantly between the two sides. As this proved not to be the case, the right splanchnic nerves were not isolated for stimulations in the subsequent experiments since it was considered very important not to traumatize the animals too much. Instead, only the great and the small splanchnic nerves on the *left* side were cautiously prepared free and isolated for direct stimulations, while at the same time the right adrenal gland was excluded. It was then assumed (and the control experiments proved this to be justified) that stimulation of the left splanchnic nerves with e. g. a frequency of four impulses per second corresponded approximately to a stimulation frequency

of the nerves on *both* sides at two impulses per second. — In order to allow electrical stimulation of the isolated left splanchnic nerves, while the abdomen was kept closed, the following procedure was used. A glass tube with a diameter of about 6 mm was closed at one end, leaving only a hole big enough to allow the entrance of the nerves. This glass tube was introduced into the abdominal cavity through a separate small opening in the left side of the abdominal wall, so that its end could be placed just above the isolated left splanchnic nerves. The peripheral ends of the nerves were then cautiously drawn up through the hole in the bottom of the glass tube and placed on an unipolar or bipolar silver electrode, introduced from above into the glass tube, after which the tube was filled with liquid paraffin at body temperature. In this way the left splanchnic nerves could be directly stimulated at known frequencies, voltage and pulse durations, avoiding spread of current through surrounding tissues or short circuits at the stimulations. The isolated nerves proved to remain excitable for many hours after the start of the preparation. A Grass Model 4 D stimulator was used for stimulation. The pulse duration was generally kept around 1—3 msec, and the voltage was increased until a maximal response for the frequency used was obtained. Generally 3 to 5 volts proved to be enough to induce a maximal effector response for any given frequency, indicating excitation of all the fibres in the nerves. Also in these experiments the hormonal component, i. e. the secretion from the left adrenal gland, could be definitely eliminated by 'tying off', or temporarily excluded by draining off its venous outflow as previously described. During such conditions, only the direct sympathetic nerves to the intestine would affect its blood flow and motility. On the other hand, the direct innervation could be selectively eliminated by cutting all nerve fibres surrounding the superior mesenteric artery, and in that case the catechol amines released from the left adrenal gland were solely responsible for the adrenergic effects on blood flow and motility of the intestinal segment.

The effects of reflex sympathetic activation and of direct splanchnic stimulation on intestinal motility and blood flow were compared with the effects induced by intravenous infusions of small, known amounts of adrenaline and noradrenaline. — The infusions were made by way of one of the femoral veins and an apparatus for constant

infusions was used. Solutions of l-adrenaline hydrochloride and l-noradrenaline hydrochloride were prepared in Tyrode solutions with a pH adjusted to 7.3 and put on ice until used. In the subsequent figures and text, all dosage values of the catechol amines infused are expressed as HCl salts.

Since it was observed early in the course of the investigation that the inhibitory responses of the intestine on reflex activation of the sympatho-adrenal system, or on direct stimulation of the splanchnic nerves, were remarkably delayed in onset, it was thought of interest to compare these inhibitory responses with the so-called intestino-intestinal inhibitory reflex (see e. g. KUNTZ and SACCOMANNO 1944). According to these authors this special reflex type should be elicited by way of a *local* reflex arch along the vascular arborizations in the mesentery. In order to make use of this local reflex for a comparative study a series of experiments was made, in which another segment of the small intestine was left *in situ*, besides that used for motility recording. In this isolated segment, only connected to the other segment indirectly by way of the mesenteric vessels and nerves, a glass tube was also inserted. This glass tube was connected to a syringe by way of a rubber tube so that Tyrode solution could be injected in order to distend the intestine. In some of the experiments, the nerve fibres along the vessels to this isolated section were cautiously prepared free, distally cut and electrically stimulated in the central direction at known frequencies in order to study the reflex effect on the motility of the other intestinal segment.

Since a reflex excitation of the vascoconstrictor fibres to the intestine often leads to considerable reductions of intestinal blood flow, it was of interest to know to what extent the blood flow decrease *per se* might influence the intestinal motility. A series of experiments was made in which an adjustable clamp was placed around either the superior mesenteric artery or the abdominal aorta just above the origin of the superior mesenteric artery. By graded occlusion of the arterial inflow, the blood supply to the intestine could thus be mechanically decreased to an extent similar to that obtained by vasocontrictor fibre activation; and the effects on the intestinal motility could be recorded. The clamp was kept in position with the aid of a special holder, and could thus be adjusted from the outside without entering the abdominal cavity.

The operative procedure described above usually lasted from 1 to 3 hours, and only such animals were used for experiments, as proved to be in good condition after the operation and had not been subject to any obvious damage to nerves or blood supply. Great care was always taken to keep the temperature constant, and even small blood losses were immediately replaced by infusion of Dextrane-Tyrode solution. When all the preparations were completed, the abdominal wall was closed by clips and the intestine was left *in situ* so that it should be as far as possible uninfluenced by external factors. The actual experiments were not started until intestinal motility and blood flow had been stabilized so far that the pronounced fluctuation from the basal level, often seen during the first half hour, had worn off.

CHAPTER III

Results

A. The effects of carotid occlusion

Experiments were performed on twenty-eight acutely vagotomized cats. The animals chosen for this particular study were those which showed evidence of marked reflex excitation of the sympathetic nervous system on carotid occlusion, with a blood pressure rise of at least 50 to 100 mm Hg.

In all the experiments the blood pressure and the intestinal motility were recorded, and in ten experiments the intestinal blood flow was continuously measured as well. In seven animals the left adrenal vein was cannulated as described on page 14, so that in the course of the experiments the venous outflow from this adrenal gland could be directed either into the circulation of the animal or temporarily excluded from the circulation and collected for later re-infusion.

The right adrenal gland had previously been extirpated in these experiments. This means that the activity of the hormonal component of the sympatho-adrenal system was reduced to *half* its capacity in these particular experiments, a fact that should be borne in mind when the results are quantitatively analysed.

Only in three out of the twenty-eight experiments of this group was it impossible to induce a definite intestinal inhibition by carotid occlusion. In the majority of the experiments carotid occlusion induced a prompt and often very pronounced reflex vasoconstriction, obvious from the blood pressure rise and the increased resistance to blood flow through the isolated intestinal segment, followed by a somewhat delayed intestinal inhibition. The latency of onset of this inhibitory response was in general 10—20 seconds. Exclusion of the remaining left adrenal gland, the other having been extirpated, completely eliminated the reflex inhibition of the intestine in all

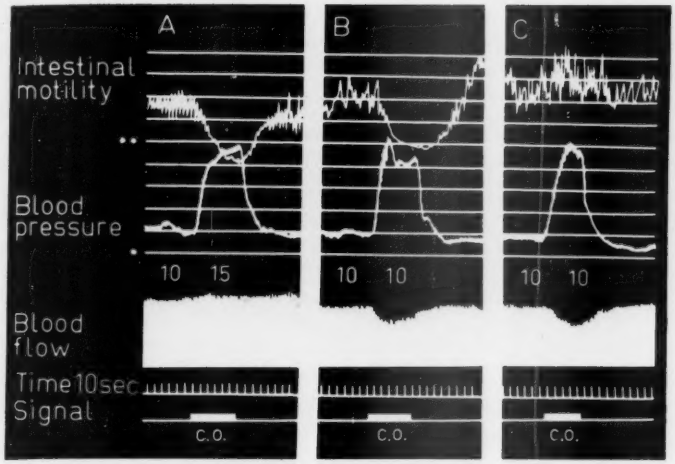

Fig. 1. Effects on intestinal motility, blood pressure and intestinal blood flow of carotid occlusion. A. Left adrenal gland intact, right adrenal gland extirpated. B. After denervation of the intestine. C. The intestine denervated and the left adrenal gland excluded. The figures above the blood flow tracing give the approximate values of the peripheral resistance in relative units. In this, and in the majority of the following figures, the blood pressure scale is indicated by one point at 100 and two points at 200 mm of mercury. The interval between two adjacent lines corresponds to 20 mm of mercury.

cases except three, where a slight inhibition could still be obtained on carotid occlusion. The intestinal inhibition was, however, largely uninfluenced by selective section of all the sympathetic nerve fibres running to the isolated intestine, provided that the innervation to the left adrenal gland via the splanchnic nerves was intact. — In those animals in which the venous outflow from the left adrenal gland was tempararily diverted out through the cannula in the adrenal vein during carotid occlusion, no intestinal inhibition was obtained in any case, even though the sympathetic nerves to the intestine were left intact. When, however, this adrenal blood was afterwards re-infused intravenously, it induced an intestinal inhibition essentially identical to that seen when the medullary secretion reached the circulation in the normal way during carotid occlusion.

Fig. 1 A shows the typical effects of carotid occlusion with an immediate and pronounced pressure response. Not until about 15

seconds later does the intestinal inhibition start and gradually reach its maximum. On removing the clamps from the carotids the blood pressure promptly decreases, while the intestinal motility returns more gradually. In this experiment the intestinal blood flow was also recorded, but it remained essentially unchanged during the period of carotid occlusion. This would mean, however, that a pronounced reflex vasoconstriction within the intestine occurred but that it was balanced by the concomitantly increased perfusion pressure so that no change in the blood flow appeared. The vasoconstrictor response becomes apparent if the peripheral resistance is calculated before, during, and after the period of carotid occlusion. It is seen from the figure that the resistance to blood flow within the intestine increased in fact by about 50 per cent during the reflex sympathetic excitation. In Fig. 1 B the same experiment was continued after section of all the nerve fibres to the intestine. The pressure response and the intestinal inhibition are almost identical with those induced before denervation of the intestine; but the vasoconstriction within the intestine is now abolished, which is obvious from the fact that the intestinal blood flow is increased approximately in proportion to the blood pressure rise, i. e. the resistance to flow within the intestine has remained unchanged during carotid occlusion. Lastly, part C in Fig. 1 demonstrates the influence of adrenalectomy on the responses induced by carotid occlusion. The pressure response and the change of the intestinal blood flow are almost the same as in part B. The intestinal inhibition previously seen during carotid occlusion does not, however, appear any longer.

Fig. 2 shows an experiment with the right adrenal gland extirpated and the left adrenal vein cannulated for temporary, circulatory exclusion as previously described. In part A, the venous outflow from the adrenal gland was allowed to reach the circulation in the normal way during carotid occlusion and the usual, somewhat delayed but marked intestinal inhibition was obtained. In part B, the venous blood from the adrenal gland was diverted out from the animal via the cannula and collected for later re-infusion. The pressure response was essentially the same as in A, but the intestinal inhibition now failed to appear. When, as shown in part C of Fig. 2, the collected venous outflow from the left adrenal gland was later on slowly infused to the animal via the femoral vein, an intestinal inhibition

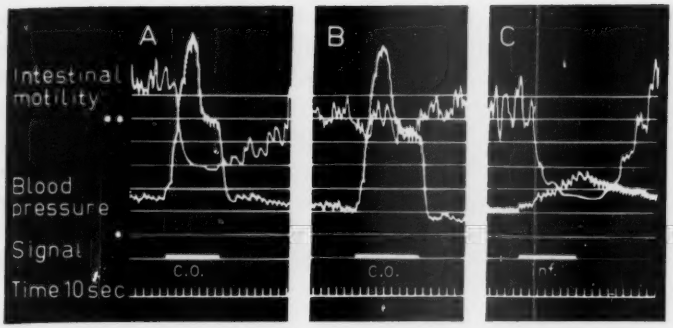

Fig. 2. Effects on intestinal motility and blood pressure of carotid occlusion. A. Right adrenal gland extirpated, left adrenal gland intact. B. The outflow from the adrenal gland diverted outside the circulation and collected. C. Infusion of the blood from the adrenal gland, collected during carotid occlusion in B.

occurred, almost identical to that seen in part A. The slight increase of blood pressure during the period of infusion was apparently caused mainly by the transfusion volume as such, 4 ml blood with 2 ml Dextrane-Tyrode solution, and not by the minute amount of catechol amines contained in it, since a comparable pressure rise was seen if 6 ml of Dextrane-Tyrode solution was infused in a similar way. Such a control transfusion, however, had no influence whatsoever on intestinal motility.

These experiments thus indicate that the intestinal inhibition induced by occlusion of the carotid arteries is practically only a consequence of the reflex increase of catechol amine secretion from the adrenal medulla, whereas the direct sympathetic innervation to the intestine appears to be of no significance in this respect. The direct sympathetic innervation, on the other hand, induces a powerful intestinal vascoconstriction, and for this response the hormonal component of the sympatho-adrenal system appears to be of little or no importance.

B. The effects of graded withdrawal of blood

For these experiments thirty-seven acutely vagotomized cats were used. Recording of intestinal motility and blood flow were arranged as previously described. In some animals the distal end of the left

adrenal vein was cannulated to allow subsequent temporary exclusions of the adrenal medullary secretion from the circulation, while the right adrenal gland was extirpated. In other cases both adrenal glands were excluded in the course of the experiments by placing ligatures around the glands. The direct sympathetic influence on the intestine could be eliminated by section of all the nerve fibres running along the vessels to the intestine. The right femoral artery and vein were cannulated in order to allow graded withdrawal and re-infusion of blood. In general the amounts withdrawn varied between 15 and 60 ml, or about 0.5—2 per cent of the body weight.

In five experiments no intestinal inhibition could be induced by withdrawal of blood, but in all other cases a significant inhibition of intestinal motility was obtained. The intestinal inhibitory response appeared generally 30 to 50 seconds after the beginning of the bleeding and disappeared as a rule under the period of re-infusion of the blood. The intestinal inhibition could not be prevented by denervation of the intestinal segment studied but was in all cases except two completely abolished after exclusion of the adrenal medullary secretion. Maximal intestinal inhibitions were sometimes observed even when such small amounts of blood were withdrawn that the intestinal blood flow was only moderately affected. — The changes in intestinal blood flow obtained in these experiments are of particular interest and will be discussed in more detail later on. In general the loss of blood caused a rapid decrease in blood pressure and a reduction of the intestinal blood flow.

Fig. 3 shows the effects generally obtained on withdrawal of blood. In part A the adrenal glands and the nervous supply to the intestine were intact. Withdrawal of 30 ml of blood caused a decrease of the blood pressure from 140 to about 80 mm Hg and an almost simultaneous reduction of the intestinal blood flow from about 20 ml to about 8 ml per minute per 100 gram of intestinal tissue. It is evident that the decrease in intestinal blood flow was to a great extent a consequence of an activation of the vasoconstrictor fibres, because the resistance to flow within the intestine increased approximately 40 per cent. The intestinal inhibition appeared in this case 50 seconds after the beginning of the bleeding and disappeared in connection with the re-infusion of the blood. In part B of Fig. 3 the nerve fibres running to the intestine had been cut, and as a

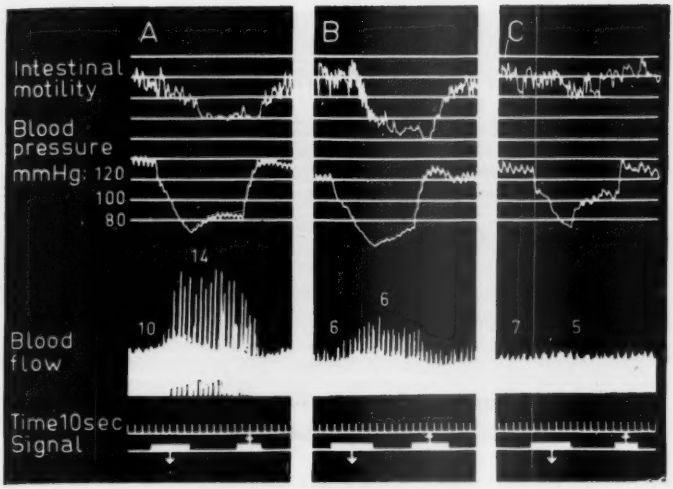

Fig. 3. Effects on intestinal motility, blood pressure and intestinal blood flow of withdrawal and re-infusion of 30 ml of blood. A. The adrenal glands and the nervous supply to the intestine intact. B. The intestinal segment denervated. C. The intestine denervated and the adrenal glands excluded. The figures above the blood flow tracing give the approximate values of the peripheral resistance in relative units.

proof of the complete denervation the resistance to blood flow was now practically uninfluenced by the loss of blood. The reduction of the intestinal blood flow appeared to be merely due to the decrease in perfusion pressure, which in part *B* had fallen to below 70 mm Hg. In part *C* of Fig. 3 the adrenal glands had been excluded, after which the experiment was continued. Withdrawal of the same amount of blood had now no influence on the intestinal motility and the intestinal blood flow remained largely unaltered. As will be illustrated in more detail in section *F*, the intestinal vessels react very sensitively to a decrease of the perfusion pressure, exhibiting a compensatory dilatation, which to some extent at least may explain the unchanged blood flow in this case. Another factor that must be considered is that in part *C* the intestinal motility was not inhibited, and under such circumstances the secondary influence of the metabolic activity of the intestine on the tone of its vascular bed would be different as compared with part *B*.

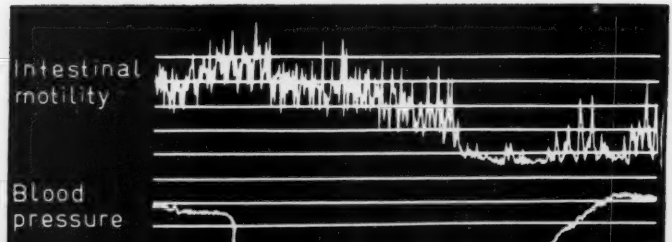

Fig. 4. Effects on intestinal motility and blood pressure of withdrawal and re-infusion of 30 ml of blood. The right adrenal gland excluded. At *a*, the venous outflow from the left adrenal gland was diverted from the circulation; at *b*, the normal, venous return was restored.

In Fig. 4 is illustrated an experiment in which the right adrenal gland was excluded and the left adrenal vein was cannulated. At *a*, the venous outflow from the adrenal gland was temporarily excluded from the circulation in the usual way while 30 ml of blood were withdrawn from the animal. The blood pressure decreased from 130 to 50 mm Hg but the intestinal motility was largely uninfluenced. At *b*, while the blood pressure was still maintained at this decreased level, the normal venous return from the adrenal gland was restored. About 20 seconds later a complete intestinal inhibition appeared. On re-infusion of the withdrawn blood, intestinal motility reappeared.

These experiments have thus shown that intestinal inhibition can be induced by acute withdrawal of blood amounting to 0.5—2 per cent of the body weight. The results indicate that this inhibition is practically entirely a consequence of the increase of catechol amine secretion from the adrenal medulla, induced by the reflex activation of the adrenal glands, when the blood pressure is acutely lowered in this way.

C. The effects of stimulation of thin afferent fibres in somatic nerves

Experiments were performed on nineteen acutely vagotomized cats, anaesthetized with nembutal or chloralose-urethane. In a few experiments the animals were decerebrated and no anaesthesia was then used except the initial ether. Recordings of intestinal motility, blood pressure and blood flow were arranged as previously described. Either the brachial plexus or the saphenous nerve of the hind limb was prepared free and cut so that the proximal end could be stimulated. In the course of the experiments, reflex changes of intestinal motility were studied after denervation of the intestine and after exclusion of the adrenal glands. In some experiments the reflex inhibition induced by afferent stimulation of somatic nerves was compared with the effect of intravenous infusion of adrenaline or with the inhibition obtained by distension of other parts of the intestine. Adrenaline was given in amounts roughly corresponding to those known to be reflexly released from the adrenal medulla on activation of 'pain fibres' (see e. g. EULER and FOLKOW 1953).

By electrical stimulation of the central ends of the brachial plexus or the saphenous nerve with frequencies of 20 to 80 impulses per second and a voltage of 5 to 15, it was in general possible to obtain reflex changes of blood pressure, respiratory movements, intestinal blood flow and of the intestinal motility. Similar effects could be induced by mechanical or thermal stimulation of the somatic nerves, procedures known to activate fairly selectively thin afferent fibres (C. v. EULER 1947). The reflex increase of the blood pressure and the intestinal vasoconstriction appeared quite promptly on afferent stimulation, while the intestinal inhibitory response was in general delayed about 15 to 30 seconds. These reflex inhibitions of intestinal motility were largely uninfluenced by postganglionic denervation of the intestinal segment studied, but could in general be completely prevented by exclusion of the adrenal glands.

Fig. 5 shows a typical experiment. In this case the central end of the brachial plexus was electrically stimulated with a frequency of 20 impulses per second and a voltage of 15. The reflex decrease in blood flow was obviously a consequence of activation of the intestinal vasoconstrictor fibres, since the resistance to flow increased from about 10 to 19 relative units. The intestinal inhibitory response,

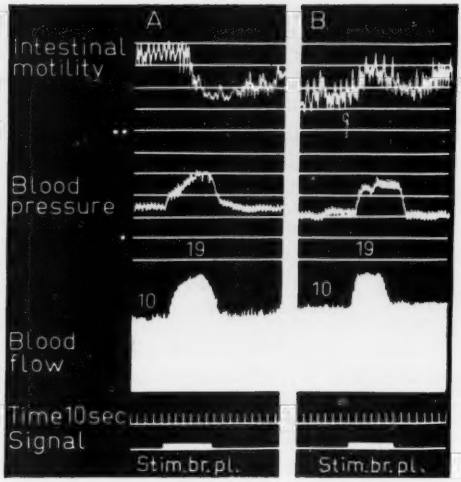

Fig. 5. Effects on intestinal motility, blood pressure and intestinal blood flow of afferent stimulation of the brachial plexus. A. Adrenal glands and nervous supply to the intestine intact. B. Adrenal glands excluded. The figures above the blood flow tracing give the approximate values of the peripheral resistance in relative units.

however, appeared first after a latency of about 25 seconds. Part *B* in Fig. 5 shows the response pattern after exclusion of the adrenal glands. The vascular effects were almost identical to those seen in part *A*, but the intestinal motility was now largely uninfluenced by the stimulation of the brachial plexus.

In Fig. 6 the intestinal inhibition caused by an intravenous infusion of 0.33 μg of adrenaline /kg body weight/ minute into the femoral vein is compared with the inhibitory response induced by electrical stimulation of the saphenous nerve. The inhibitory responses obtained were very similar in character; the latency of the onset of inhibition caused by the infusion was about 20 seconds, and that caused by afferent nerve stimulation was about 15 seconds.

In the following chapter, comparisons between the inhibitory responses induced by stimulation of thin afferent fibres and by distension of another isolated part of the intestine will be described.

The results here obtained suggest that the intestinal inhibition

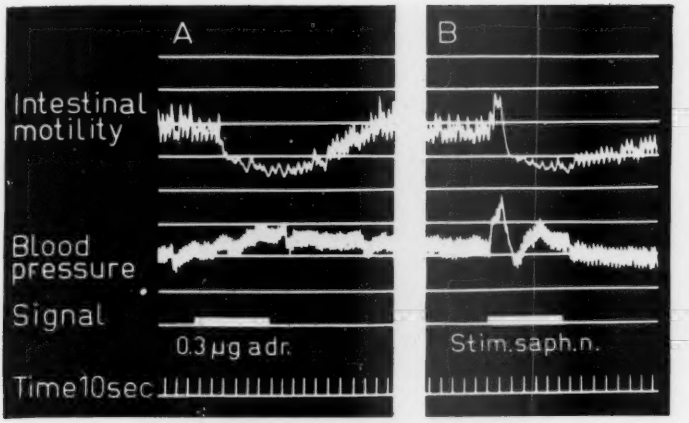

Fig. 6. Comparison between the intestinal inhibitory responses induced by intravenous infusion of adrenaline and by afferent stimulation of the saphenous nerve. A. Infusion of 0.33 µg of l-adrenaline/kg/minute in the femoral vein. B. Electrical stimulation of the saphenous nerve with a frequency of 80 impulses per second and a voltage of 5.

seen on stimulation of thin afferent fibres in somatic nerves is a consequence of the increased secretion of catechol amines from the adrenal medulla.

In the course of this investigation, where it was of especial interest to keep the level of anaesthesia as superficial as possible, it was found that the level of the anaesthesia itself had a pronounced influence on the intestinal motility. When a superficial anaesthesia was used, for instance in order to allow strong reflex excitations of the sympatho-adrenal system, the intestinal motility was already in general considerably depressed to start with. The motility could often be markedly enhanced if additional anaesthesia was given so that the reflex sympathatic activity was depressed, or if the adrenal glands were excluded. Attempts were made to use decerebrate, unanaesthetized cats in some experiments, but it was found that the continuous activity of the sympatho-adrenal system was here in many cases strong enough to almost completely depress intestinal motility, presumably by way of an increased secretion from the adrenal medulla.

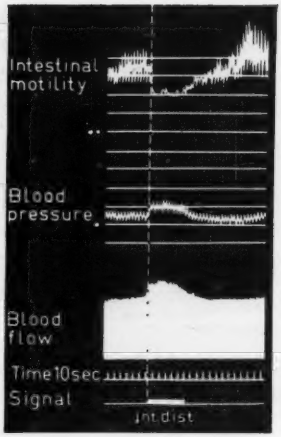

Fig. 7. Effect on the motility in one intestinal segment caused by distension of another intestinal loop. Adrenal glands excluded and splanchnic nerves sectioned.

D. The intestino-intestinal inhibitory reflex

Experiments were performed on seven acutely vagotomized cats. Recording of blood pressure and of intestinal motility from a jejunal loop was arranged in the usual way. In some of the experiments intestinal blood flow was recorded as well. Another small intestinal loop was prepared for distension or electrical stimulation of its periarterial nerves as previously described.

It was found that an immediate and intense intestinal inhibition could regularly be induced by distension of another, isolated part of the intestine and that this inhibitory response, the so-called intestino-intestinal inhibitory reflex, remained unimpaired when the adrenal secretion was eliminated and also when all the splanchnic nerves were cut. The nerve ramifications along the mesenteric vascular branches, however, had to be left intact. The rapidity of onset was typical of a truly neurogenic reflex mechanism. This reflex inhibition was easily reproduced also by direct afferent stimulation of the periarterial nerve fibres from the distended intestinal loop with frequencies well below ten impulses per second.

Fig. 7 shows the immediate and pronounced inhibition of intestinal

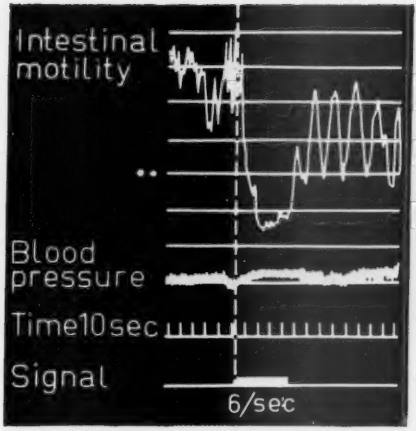

Fig. 8. Electrical stimulation of the afferent link of the intestino-intestina inhibitory reflex arch. Stimulation frequency 6 impulses per second.

motility induced by distension of the other isolated intestinal segment. The slight reduction of the intestinal blood flow and the minute rise of the blood pressure seen in the figure appear to be due simply to the mechanical influence of the distension on the blood flow, since the blood flow recording also included the distended loop.

Fig. 8 shows that direct stimulation of the mesenteric nerves from an isolated loop gave rise to a response similar to that caused by distension of the loop, namely an immediate and pronounced inhibition of the other intestinal segment.

An experiment in which the intestino-intestinal inhibitory reflex was compared with the inhibitory response induced by excitation of 'pain fibres' is demonstrated in Fig. 9. In part *A* of the figure, when the adrenal glands and the nervous supply to the intestine were still intact, the two procedures — intestinal distension and mechanical stimulation of brachial nerves — both induced intestinal inhibitions which were similar in magnitude but which showed important differences in the onset of the responses. While the response on intestinal distension was immediate in onset, the inhibition induced by activation of 'pain fibres' was delayed, in this case about 15 seconds. The reflex vasoconstrictor response, as indicated

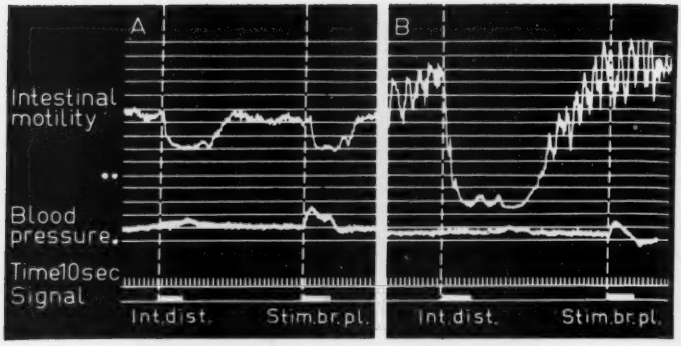

Fig. 9. Comparison between the inhibitory responses induced by intestinal distension and by mechanical stimulation of the brachial plexus. A. The adrenal glands and the nervous supply to the intestine intact. B. The adrenal glands excluded.

by the rise in blood pressure, was, however, as usual prompt in onset. Part *B* of Fig. 9 shows a repetition of the same procedures after exclusion of the adrenal glands. The intestinal motility was now considerably increased, presumably as a result of the elimination of a basal adrenal medullary secretion. The inhibitory response to distension of the gut was prompt and pronounced, but the intestinal motility was now uninfluenced by the activation of pain fibres.

As regards the intestino-intestinal inhibitory reflex, the present results are in agreement with the findings of KUNTZ and SACCOMANNO (1944). It seems as if this type of local reflex inhibition is elicited by way of a system strictly localized in the periphery, and this is apparently not controlled by central sympathetic structures, since direct stimulation of the splanchnic nervous outflow with low frequencies only elicits a delayed inhibitory response, which is eliminated when the adrenal glands are excluded (see also section *E*). By comparing this local reflex with the reflex intestinal inhibition induced by activation of 'pain fibres', where the splanchnic nerves form the efferent pathway, it was found that the latter response, like that obtained on direct splanchnic stimulation, had a considerable latency of onset, which indicates that it is due to discharge of catechol amines from the adrenal medulla.

E. The effects of graded electrical stimulation of the splanchnic nerves

In this series, experiments were performed on twenty-two acutely vagotomized cats. Blood pressure, intestinal motility and intestinal blood flow were continuously recorded throughout the experiments. The right adrenal gland was excluded from the circulation and the left splanchnic nerves were cautiously dissected free and cut centrally, after which their distal ends were put on the stimulating electrode. Except for a few control experiments the right splanchnic nerves were not prepared for stimulation, since this preparation is technically very difficult and implies a considerable additional traumatization of the animal. It was then assumed, for reasons given previously, that unilateral stimulation of the splanchnic nerves with e. g. a frequency of 4 impulses per second would give about the same effects as bilateral splanchnic stimulation with a frequency of 2 impulses per second. In the text and in the figures, the frequencies actually used at the unilateral stimulation are given. The upper limit of stimulation frequency used was set at 16 impulses per second and the total period of stimulation was generally restricted to one minute. Direct stimulation of the left splanchnic nerves was performed partly with the nervous connections to the left adrenal gland and to the intestine intact, partly after selective exclusion of the adrenal gland or after post-ganglionic denervation of the intestine. The consequent changes in intestinal motility and blood flow were then compared. In some experiments, intestino-intestinal inhibitory reflexes were induced and compared with the inhibitory responses induced by splanchnic stimulation, in respect of magnitude, latency of onset and other characteristics.

It was found that on left splanchnic nerve stimulation a practically maximal intestinal inhibition could be induced with frequencies as low as 2—4 impulses per second, as long as the left adrenal gland was left intact. The latency of onset of this intestinal inhibition was about 15 seconds, a time period which corresponds quite well with the circulation time from the adrenal gland to the intestine. In contrast to this considerable delay, the onset of the intestinal vaso-constrictor response during splanchnic nerve stimulation was always prompt. Section of the nervous supply to the intestine did not influence the inhibitory responce but completely abolished the

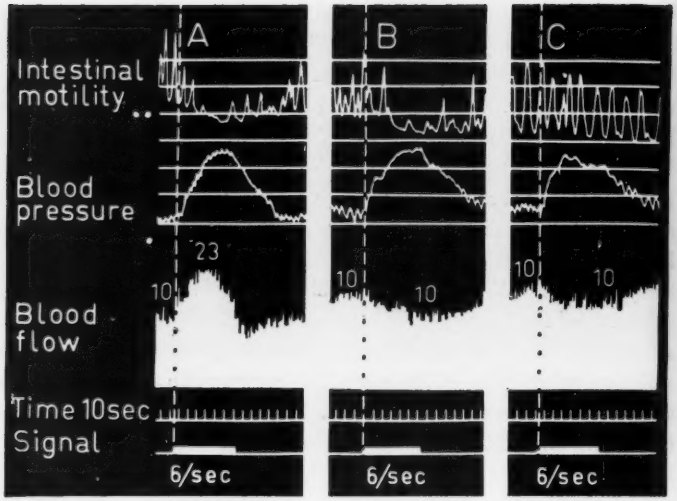

Fig. 10. Effects on intestinal motility, blood pressure and intestinal blood flow of electrical stimulation of the left splanchnic nerves. A. The left adrenal gland and the nerve supply to the intestine intact. B. After denervation of the intestine. C. The intestine denervated and the left adrenal gland excluded. The figures above the blood flow tracing give the approximate values of the peripheral resistance in relative units.

intestinal vasoconstrictor response. When, on the other hand, the adrenal secretion had been selectively excluded, splanchnic nerve stimulation produced the opposite result, that is, a prompt and pronounced vasoconstriction occurred, whereas practically no inhibition of intestinal motility was seen, except when 'supraphysiological' stimulation frequencies, i. e. above 8—10 impulses per second, were used.

The general findings are illustrated in Fig. 10. In part A of this figure the left adrenal gland as well as the nerve supply to the intestine were intact. Stimulation of the left splanchnic nerves with a frequency of 6 impulses per second induced a prompt intestinal vasoconstriction, increasing the resistance to flow about 130 per cent, and after a latency of about 15 seconds a considerable intestinal inhibition also occurred. In part B of Fig. 10 all the nerve fibres to the intestine had been sectioned, and as an evidence of the intestinal denervation

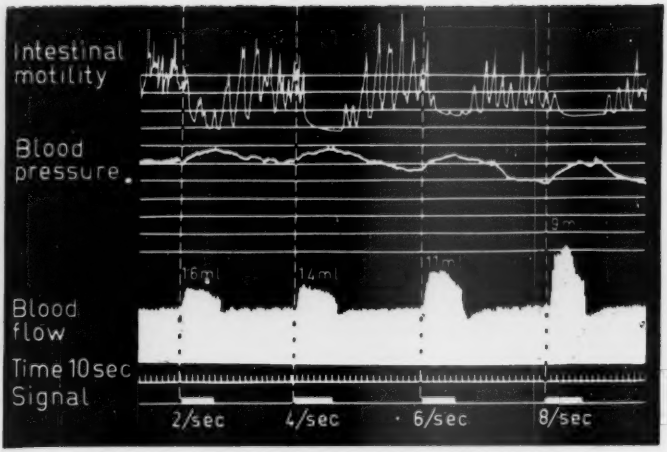

Fig. 11. Effects on intestinal motility, blood pressure and intestinal blood flow of splanchnic nerve stimulation with progressively increasing frequencies. The left adrenal gland and the nerve supply to the intestine intact. The figures above the blood flow tracing give the intestinal blood flow in ml/minute/100 grams of intestinal tissue.

splanchnic nerve stimulation did not change the resistance to blood flow within the gut. The inhibition of intestinal motility induced by the splanchnic nerve stimulation, on the other hand, was essentially unchanged. When the left adrenal gland was also excluded, however, splanchnic stimulation no longer influenced the motility of the intestine (part C). The rise in blood pressure is secondary to the vasoconstrictor effects on the spleen, the stomach and the liver.

In Fig. 11, the responses induced by splanchnic nerve stimulation at progressively increasing frequencies are illustrated. In this experiment, both the left adrenal gland and the nerve supply to the intestine were left intact. A significant intestinal inhibition was obtained already at a stimulation frequency of 2 impulses per second and the response was practically at its maximum at 4 impulses per second, but it appeared first after a delay of about 10—15 seconds. The vasoconstrictor responses, here expressed as the actual blood flow values in ml/minute/100 gr intestinal tissue, were always prompt in onset; but, in contrast to what was the case with the intestinal inhibitory responses, the vasoconstrictor responses continued to

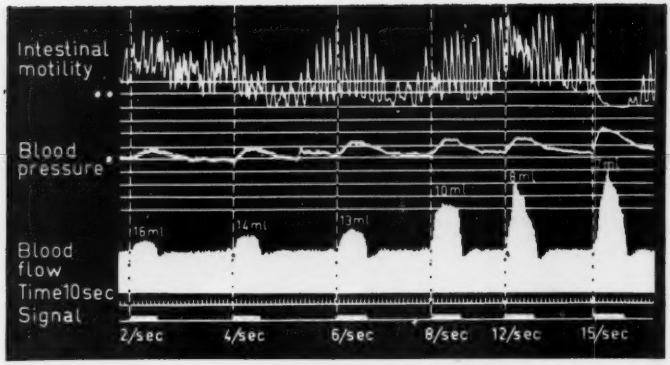

Fig. 12. The experiment of Fig. 11 repeated after exclusion of both adrenal glands.

increase with further increase of the stimulation frequency. — Fig. 12 shows the same experiment after the left adrenal gland had also been excluded. The vasoconstrictor responses were still prompt and of about the same magnitude as in Fig. 11, but the lower frequencies had no effect on intestinal motility. In this experiment inhibition did not occur until a frequency of 15 impulses per second was reached.

In Fig. 13 and 14, the inhibitory response induced by direct stimulation of the left splanchnic nerves at six impulses per second is compared with that obtained on distension of another part of the intestine. The two inhibitory reactions were almost similar in magnitude, but while the inhibition caused by splanchnic stimulation appeared first after a considerable latency, in this case 20 seconds, the inhibition following distension was immediate in onset. This was also the case if the central ends of the sectioned nerve filaments, running from the distended segment of the intestine, were stimulated at the same rate.

These experiments thus indicate that the intestinal inhibition obtained by direct stimulation of the splanchnic nerves with frequencies within the sympathetic physiogical discharge range is almost entirely due to the release of hormones from the adrenal medulla. The latency of onset of this inhibition corresponds fairly well with the circulation time from the adrenal medulla to the intestine, and the response is abolished by exclusion of the glands. This delayed

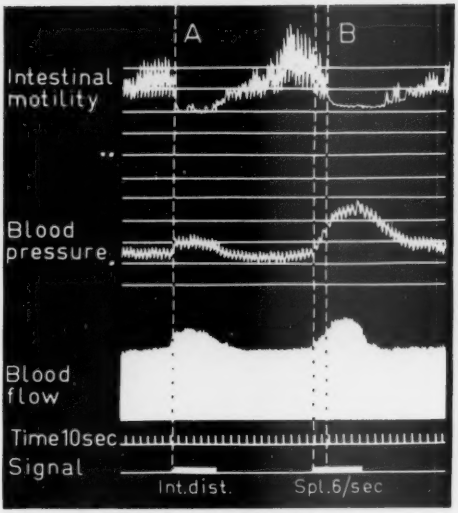

Fig. 13. The intestino-intestinal inhibitory reflex compared with the inhibitory response induced by direct stimulation of the left splanchnic nerves at a frequency of 6 impulses per second. The left adrenal gland and the nerve supply to the intestine intact. See also Fig. 14.

inhibitory response is therefore of another nature than the prompt inihibition caused by the intestino-intestinal inhibitory reflex, also seen when this local reflex arch is electrically activated at very low frequencies. The intestino-intestinal reflex is not dependent on the sympathetic innervation via the splanchnic nerves, since it remains essentially unchanged even when all known preganglionic fibres are cut. The response is not abolished until the nerve ramifications along the vascular branches to the intestine are destroyed. The adrenal glands being eliminated, stimulation of the splanchnic nerves with, say, 6 impulses per second does not elicit any intestinal inhibition, whereas a prompt and powerful inhibition is readily induced when the nervous structures forming the pathways of the intestino-intestinal reflex are stimulated at the same rate. It therefore seems as if the preganglionic splanchnic fibres do not make any contact with the nerve elements responsible for the intestino-intestinal reflex.

After exclusion of the adrenal glands, intestinal inhibition could be

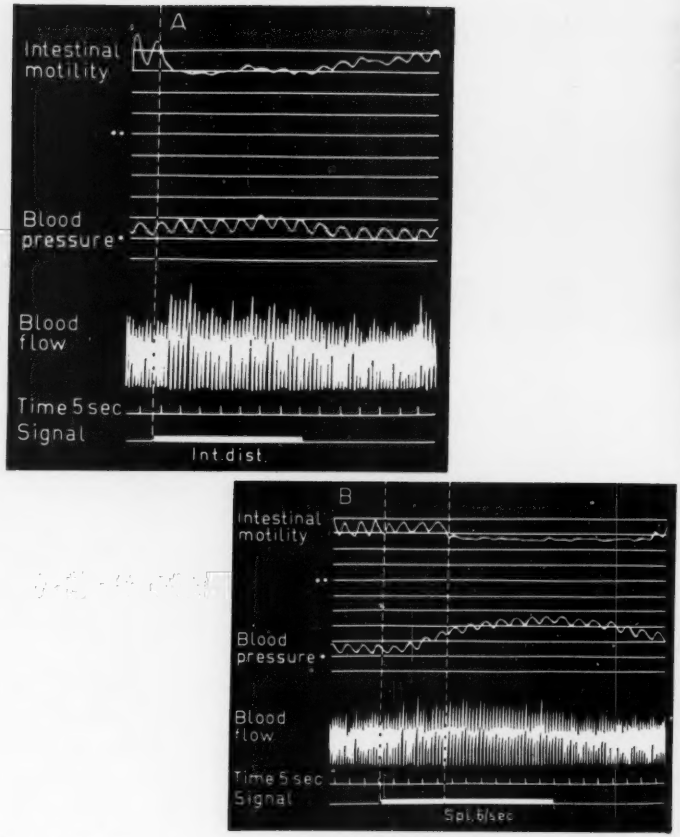

Fig. 14. The same experiment as shown in Fig. 13, but recorded at a higher kymograph speed.

induced by splanchnic nerve stimulation only when frequencies above 8—10 impulses per second were used. As mentioned previously, however, an 'overflow' of the transmitter from the vasoconstrictor nerve endings is known to take place under these conditions. This overflow, alone or in conjunction with the reduction of the blood supply to the gut, may very well be responsible for the intestinal inhibition seen at high frequency stimulation of the splanchnic nerve fibres.

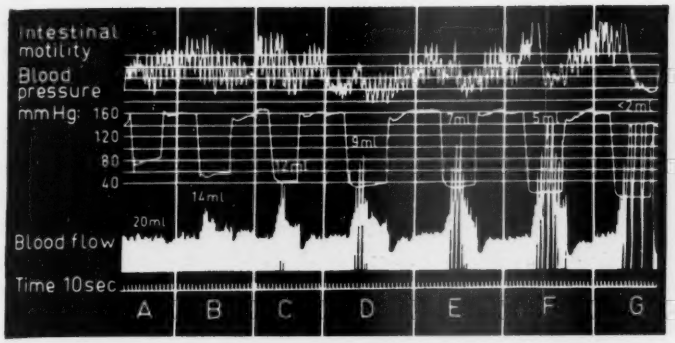

Fig. 15. Effects on the intestinal motility and intestinal blood flow of mechanical reductions of the arterial inflow to the intestine. The adrenal glands were excluded and the nerve supply to the intestine interrupted. A screw-clamp was placed around the aorta. The figures above the blood flow tracing give the intestinal blood flow in ml/minute/100 grams of intestinal tissue.

F. The effects of mechanically induced reduction of the intestinal blood flow

Twenty-one cats were used in these experiments. Both adrenal glands were excluded and the nerves to the intestine were cut. The intestinal motility and blood flow were recorded and a screw-clamp was placed around the aorta or the superior mesenteric artery. Some of the experiments were performed on animals in which reduction of blood flow was also induced by direct stimulation of the peripheral ends of the sectioned left splanchnic nerves. The effect on motility of mechanical obstruction of blood flow could thus be compared with that induced by stimulation of vasoconstrictor nerves to the intestine.

It was found that an intense intestinal inhibition could be obtained when a reduction of the blood supply to the intestine was mechanically induced. This decrease in intestinal blood flow had to be quite pronounced, however, before the intestinal motility was significantly affected.

Fig. 15 shows an experiment in which the screw-clamp was placed around the aorta just above the origin of the superior mesenteric artery. The blood pressure was recorded from the left femoral artery and therefore this tracing gives the approximate arterial inflow pressure in the intestinal vessels. It will be seen from the figure that

a decrease of the perfusion pressure from 160 to 80 mm Hg had practically no influence on the intestinal blood flow, which indicates that the acutely denervated intestinal blood vessels were compensatorily widened, roughly in proportion to the reduction of the pressure. By further reduction of the perfusion pressure the intestinal blood flow was increasingly reduced, but the perfusion pressure had to be decreased to a level below 40 mm Hg before any significant intestinal inhibition appeared. At this low perfusion pressure, the intestinal blood flow was initially excessively decreased, as seen in the figure, but a compensatory vascular dilatation seems to take place in these extreme cases also. This is apparent from the fact that the initially intense reduction of the blood flow rapidly subsided in spite of the constantly lowered arterial inflow pressure. The recordings indicate that the smooth muscles of the intestinal blood vessels start to relax at less drastic blood pressure and flow reductions than those needed to initiate a significant decrease in intestinal motility. A complete inhibition of the intestine was first obtained when the blood flow was decreased to less than ten per cent of the initial flow values (compare G with A in Fig. 15).

To sum up: Inhibition of intestinal motility could be induced by mechanical obstruction of the blood supply to the intestine, but it was generally necessary to reduce the blood flow to roughly 25 per cent of its initial value before any significant inhibition appeared. There is therefore reason to believe that the reduced blood supply as such affects the intestinal motility by way of the consequent change in the local environment of the smooth muscle. It is probable that this mechanism contributes to the intestinal inhibition seen when the sympathetic vasoconstrictor fibres are so intensely activated that a serious reduction of the blood supply takes place. The vascular smooth muscles appear to be more sensitive to these secondary environmental changes than those of the intestinal wall, since a partial obstruction of the arterial inflow more readily induced a vasodilatation than an inhibition of the intestinal motility.

G. The effects of intravenous infusion of catechol amines

The inhibitory effects of l-adrenaline and l-noradrenaline on the intestinal motility were quantitatively studied in ten experiments, in which the drugs were infused intravenously in amounts corres-

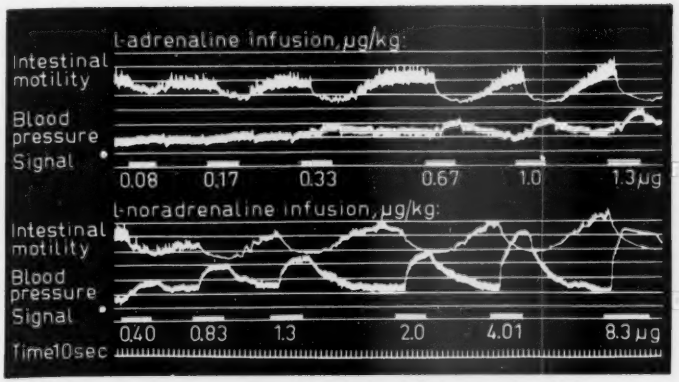

Fig. 16. Effects on intestinal motility and blood pressure of intravenous infusions of l-adrenaline and l-noradrenaline in successively increasing amounts. The doses of catechol amines infused are expressed in µg/kg body weight/minute.

ponding to those secreted from the adrenal glands when activated at stimulation frequencies within the 'physiological' range. Furthermore, the effects of single infusions were compared with those obtained by the procedures described in earlier chapters. Blood pressure and intestinal motility were recorded in all cases, and in some experiments intestinal blood flow was studied as well. The degree of inhibition obtained by different doses of catechol amines was expressed as an approximate percentage of the maximal inhibition, i. e. the inhibitory response obtained with supramaximal doses. In earlier studies by CELANDER (1954), as mentioned in Chapter I, it was shown that in cats about 5 µg of catechol amines/kg of body weight/minute are released when *all* the cells of the two adrenal medullas are activated simultaneously at ten impulses per second. The doses of catechol amine infused were kept below this assumed upper limit for hormone release at maximal reflex sympathetic activation. Assuming that the amount of catechol amine released per stimulation shock is fairly constant, this means that at a discharge rate of 1 impulse per second approximately 0.5 µg/kg/minute is released in the average cat if all the adrenal medullary cells are activated.

Fig. 16 illustrates the general findings in these experiments. An infusion of as little as 0.08 µg of l-adrenaline/kg body weight/minute

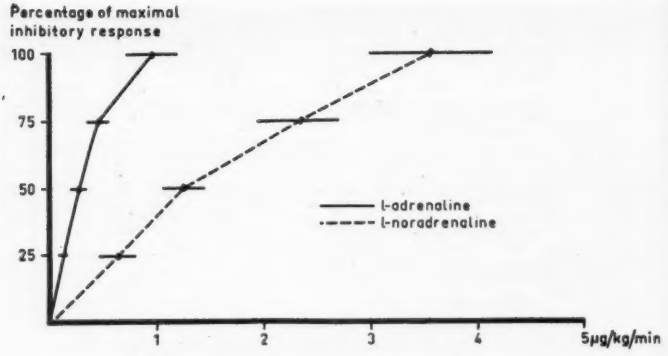

Fig. 17. Mean curves of the approximate intestinal inhibition obtained by infusion of catechol amines in successively increasing amounts. The horizontal bars through the points give the standard deviation of the mean amounts of catechol amines calculated on ten experiments.

caused a significant depression of intestinal motility but had no noticeable influence on the blood pressure. In this particular experiment, an almost maximal intestinal inhibition was obtained even with 0.67 μg/kg/minute of adrenaline, a dose which only slightly affected the blood pressure. L-noradrenaline had to be infused in amounts 3 to 5 times bigger in order to induce corresponding degrees of intestinal inhibition, but the blood pressure responses were considerably larger in this series of infusions.

The results of the experiments are summarized and illustrated graphically in Fig. 17. The smallest average amounts needed to induce a noticeable intestinal inhibition were 0.13 μg/kg/minute for l-adrenaline and 0.64 μg/kg/minute for l-noradrenaline.

Fig. 18 shows the inhibitory effects obtained when l-adrenaline and l-noradrenaline were infused in equal amounts. In part A, 2.4 μg of l-adrenaline/kg/minute caused complete motor inhibition, whereas the resistance to blood flow within the intestine increased only about 30 per cent. In part B, when the same amount of l-noradrenaline was infused the vascular effects were much more pronounced, with a more than 100 per cent increase of flow resistance, but the intestinal inhibition was considerably weaker than that induced by adrenaline.

The experiments described in this chapter have shown that the

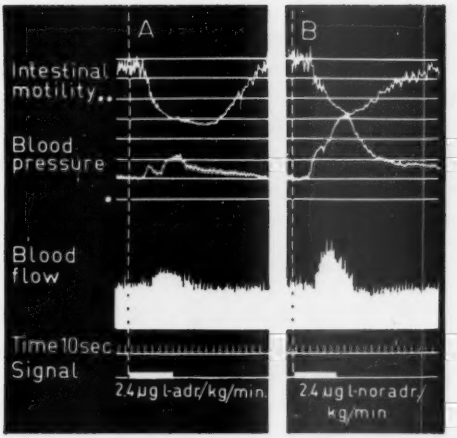

Fig. 18. Effects on intestinal motility, blood pressure and intestinal blood flow of intravenous infusions of equal amounts of l-adrenaline and l-noradrenaline.

average threshold for intestinal inhibition was reached when 0.13 µg/kg/minute of l-adrenaline was infused intravenously. No demonstrable effects on the blood pressure or intestinal blood flow were seen with this rate of infusion. The threshold dose for l-noradrenaline was about 5 times higher with regard to intestinal inhibition, but considerably lower where vasoconstriction was concerned. A practically maximal intestinal inhibition was generally obtained with 1—1.2 µg of adrenaline/kg/minute, an amount which would roughly correspond to the amount of catechol amines released from the two adrenal glands when all their cells are activated at a rate of around 2 impulses per second. This rate of secretion is well below the upper limit for maximal adrenal medullary discharge, seen at intense reflex activation of the sympatho-adrenal system.

CHAPTER IV

General Discussion

The major aim of this study was to investigate which of the theoretically possible mechanisms for inducing reflex intestinal inhibition are the most important ones, and thus to investigate in what way central inhibitory control of intestinal motility is brought about. In the previous chapter the results have been only briefly commented upon, and a more detailed discussion is therefore necessary.

It might be objected that the results obtained under the present experimental conditions are not necessarily representative of the reactions in conscious intact animals. The experiments were so arranged, however, that comparative analyses, allowing quantitative estimations, could be made in one and the same animal, with the aid of methods for selective exclusions of the different components of the sympatho-adrenal system. The effects of one procedure could thus be subjected to control by comparison with the others. It therefore seems unlikely that the present evaluation of the interrelationship of the inhibitory components studied, would have been disturbed to any significant extent by such factors as the anaesthesia or the operative procedures.

By carotid occlusion, by graded withdrawal of blood, and by activation of thin afferent fibres in somatic nerves it was possible to induce reflex intestinal inhibitions which showed some important common characteristic features. For instance, the inhibitory responses were always somewhat delayed, in contrast to the promptly appearing vascular responses of the intestine induced by the same type of reflex stimulation. The inhibitory responses were practically uninfluenced by perivascular denervation of the intestine, provided that the adrenal glands and their innervation via the splanchnic nerves were left intact. When on the other hand the adrenal glands were excluded,

the inhibitory responses disappeared. These procedures produced the opposite effect on the vascular responses, which were abolished by denervation and largely uninfluenced by exclusion of the adrenal glands. If the venous effluent from the adrenal glands, collected during reflex stimulation, was afterwards re-infused into the animal, an intestinal inhibition appeared which was essentially identical with the one seen during reflex stimulation with the adrenal glands intact. Similar inhibitory responses could be induced by intravenous infusion of catechol amines in amounts corresponding to those released on reflex activation of the adrenal medulla.

Practically all autonomic effectors in the cat respond promptly to nerve stimulations. The dilator muscle of the iris and the nictitating membrane may even produce a definite response to a single shock stimulus, and the effector responses to reflex activation or to direct stimulation of vasoconstrictor fibres are always immediate. The pronounced delay of the intestinal inhibitory responses in the above mentioned experiments is therefore remarkable, particularly when compared to the strikingly prompt onset of the response when the so-called intestino-intestinal inhibitory reflex is induced. Such a delay of a particular effector response in a reflex pattern, where all other directly innervated effectors are immediately engaged, is hardly compatible with the conception that the response is induced by centrally controlled, specific inhibitory nerve fibres. The delay cannot be ascribed to a sluggishness of the effector cells themselves, since they are able to respond promptly in other circumstances, e. g. when engaged in the intestino-intestinal inhibitory reflex or when exposed to close intra-arterial injections of catechol amines. It therefore seems improbably that the intestinal inhibition obtained by reflex activation of the sympatho-adrenal system *via* the central nervous system would be induced by way of any centrally controlled inhibitory fibres in direct contact with the intestinal smooth muscles. If that were so, one would have to accept the idea that there exist neuroeffector junctions operating with a latent period amounting to about 15 seconds. Further, the fact that this delayed inhibitory reflex response is eliminated by exclusion of the adrenal medullary secretion strongly supports the assumption that this type of reflex inhibition is mediated *via* the adrenal medulla and not by way of specific inhibitory nerve fibres in the splanchnic nerves.

It is known that the intestinal smooth muscles are very sensitive to adrenaline, administered by way of the blood stream, and in section G of Chapter III it was shown that a significant intestinal inhibition could be obtained in cats by intravenous infusions of adrenaline in doses below those necessary to affect blood pressure or intestinal vasomotor tone. In this respect, as in many others, adrenaline shows a considerable quantitative difference from noradrenaline, whose inhibitory effect on the intestinal smooth muscles was found to be only one-third to one-fifth of that of adrenaline. The amounts of adrenaline necessary to induce a maximal inhibition of intestinal motility, are quite comparable to those released to the blood stream during reflex sympathetic activation. According to the data of CELANDER (1954), a blood concentration of catechol amines of corresponding magnitude is obtained during activation of all the medullary cells at a frequency as low as two impulses per second. The functional differentiation of the two hormones from the adrenal medulla seems to be well established by recent investigations (see EULER 1956, 1958). The adrenaline secretion, besides its effect on metabolic processes, thus seems to be mainly responsible for the centrally induced depression of intestinal motor activity, known to occur during generalized excitation of the sympatho-adrenal system.

Further evidence indicating the importance of the hormonal component as a mediator of centrally induced intestinal inhibition is presented in section E of Chapter III. It was shown that as long as the adrenal glands were intact direct splanchnic nerve stimulation induced an almost maximal, though always delayed, intestinal inhibition even at frequencies as low as 1 to 2 impulses per second and, further, that these inhibitory responses were not affected by perivascular denervation of the intestine. The inhibitory responses obtained after interruption of the nervous supply to the intestine could not be explained by incomplete denervation, since the vasoconstrictor responses were completely abolished after section of the nerve fibres. Further, the inhibitory responses were eliminated by exclusion of the adrenal glands. The latency of onset of this inhibition was in general about 15 seconds, a period of time which corresponds fairly well with the circulation time from the adrenal glands to the intestine. Contrary to this delayed inhibitory response,

the intestinal vasoconstriction obtained by splanchnic nerve stimulation was always prompt in onset.

When the dominating inhibitory influence of the hormonal component is excluded and the inhibitions then induced by splanchnic nerve stimulations are analysed, the present results confirm the findings of CELANDER regarding the question of a central, specific inhibitory control of the intestine via the splanchnic nerves (see section E and F of Chapter III). In the present study only the left splanchnic nerves were stimulated in most cases. When this was performed with low impulse frequencies, well within the physiological discharge rates, relatively weak vasoconstrictor effects were induced, as compared with those reported in CELANDER's study, which is quite natural as only half the amount of nerve fibres were activated. These relatively moderate vasoconstrictor responses were only exceptionally accompanied by a weak, delayed inhibitory response; in most cases the motility was unchanged. After exclusion of the adrenal secretion it was possible to induce significant and relatively prompt intestinal inhibitions by splanchnic nerve stimulation only if frequencies of stimulation above 8—10 impulses per second were used. At such rates of discharge, however, where drastic reductions of intestinal blood flow appear, an overflow of the constrictor fibre transmitter is known to occur (CELANDER 1954, BROWN and GILLESPIE 1957 and BROWN, DAVIES and GILLESPIE 1958). This overflow seems to be able to inhibit the tone of the smooth muscles. — The mere reduction of the blood supply will undoubtedly contribute to the inhibitions then seen, but quite drastic vasoconstrictions appear to be needed under such circumstances. This is evident from the results described in section F of Chapter III, where it was found that the arterial inflow to the intestine had to be reduced to at least 25 per cent of its prevailing magnitude before this factor alone could induce any significant intestinal inhibition. Celander has discussed in detail this mechanism and the effect of transmitter overflow for inducing intestinal inhibition (see CELANDER 1959). In his analysis of the evidence against the existence of specific inhibitory fibres in the splanchnic nerves, however, he did not deal with the relative importance of the hormonal component of the sympathoadrenal system. The results of the present investigation strongly suggest that the hormonal component is by far the most potent

factor in inducing inhibition of intestinal motility. The inhibitory effect of the reduced blood flow *per se* or of the transmitter overflow will be hardly of any significance before extreme reflex excitations of the sympathetic nervous system are elicited, but by then the hormonal component will have already induced a maximal inhibition of intestinal motility. There is good evidence to believe that normally the discharge rate of autonomic fibres practically never surpasses the rate of about 8—10 impulses per second (FOLKOW 1956). This may very well explain much of the variety of the findings obtained in earlier investigations. The majority of the results previously presented as evidence in favour of the existence of specific inhibitory fibres in the splanchnic nerves can readily be explained as due to the use of stimulation frequencies above the physiological discharge rates, causing an overflow of the vasoconstrictor fibre transmitter.

Another factor that will help to explain the contradictory results in many earlier studies of the inhibitory control of intestinal motility is the existence of a peripherally localized, inhibitory reflex arch, the intestino-intestinal inhibitory reflex. Stimulation of periarterial nerve bundles, peripherally to the coeliac ganglion, will activate the efferent link of this reflex arch, which follows the mesenteric vascular arborizations. Judging from the present study, this reflex does not appear to be influenced by any centrally controlled fibres, since splanchnic stimulation at low rates never induced any intestinal inhibition when the adrenal secretion was excluded. The intestino-intestinal inhibitory reflex arch should therefore not be looked upon as a part of the sympathetic nervous system, if by this conception is meant the centrally controlled thoraco-lumbar outflow of the autonomic nervous system.

Summary

The present study was performed with the aim of investigating what mechanisms are employed in eliciting the reflexly induced inhibition of intestinal motility, and thus how the central inhibitory control of intestinal motility is brought about. The following four essentially different modes of action were considered:

1) A centrally controlled specific inhibitory innervation of the intestinal smooth muscles.
2) An 'overflow' of the vasoconstrictor fibre transmitter, inducing an inhibitory action on adjacent intestinal smooth muscle cells.
3) A shift in the local chemical environment of the intestinal smooth muscle, secondary to the reduction in blood supply brought about by sympathetic vasoconstrictor activity.
4) An increased secretion of catechol amines from the adrenal medulla, induced by splanchnic nerve fibre activation and reaching the intestinal smooth muscle cells by way of the blood stream.

The experiments were performed on acutely vagotomized, anaesthetized cats and arranged so that intestinal motility could be recorded in a jejunal loop *in situ*. The blood pressure and the intestinal blood flow were also recorded. In order to induce reflex excitations of the sympatho-adrenal system the experimental animals were exposed to occlusion of the carotid arteries, graded withdrawal of blood, and electrical or mechanical stimulation of thin afferent fibres in somatic nerves. In the course of these procedures for inducing reflex inhibition of the intestinal motility, the effects of exclusion of the adrenal secretion and of denervation of the intestinal segment on intestinal motility and blood flow were studied. The reflexly induced responses were also quantitatively compared with the effects obtained by electrical stimulations of the splanchnic nerves, with or without exclusion of the adrenal glands, and with

the intestino-intestinal inhibitory reflex. Further, the inhibitory effects on intestinal motility of intravenous infusion of catechol amines were studied and, lastly, graded reductions of the intestinal blood supply were mechanically induced.

It was found that the inhibitory responses induced by carotid occlusion, by withdrawal of blood and by stimulation of afferent somatic nerves were not noticeably affected by denervation of the intestine. In practically no case, however, could inhibitory responses be obtained after adrenalectomy, or when the venous blood from the adrenal glands was diverted from the general circulation. By re-infusion of the adrenal venous blood thus collected, an intestinal inhibition appeared which was essentially identical with that obtained when the adrenal circulation was intact.

As long as the adrenal glands were intact, direct splanchnic stimulation induced an almost maximal intestinal inhibition at frequencies as low as 1—2 impulses per second. The latency of the onset of this inhibition corresponded to the circulation time from the adrenal glands to the intestine. Contrary to this delayed, but pronounced inhibitory response, the intestinal vasoconstriction was always prompt. The inhibitory responses obtained by stimulation of the splanchnic nerves with low frequencies could be prevented by exclusion of the adrenal glands, and they thus appear to be almost entirely a result of the activation of the adrenal medullary cells.

After exclusion of the adrenal glands, splanchnic stimulation still induced a prompt and undiminished vasoconstrictor response; but in general it was now necessary to use frequencies above 8—10 impulses per second to induce any significant intestinal inhibition. There are strong reasons for believing that this inhibitory response to high frequency stimulation is partly a consequence of an 'overflow' of the transmitter substance at the vasoconstrictor nerve endings, and partly due to the now marked reduction in intestinal blood supply induced by the intestinal vasoconstrictor fibres.

In striking contrast to the delayed intestinal inhibition, seen on direct stimulation of the splanchnic nerves at 'physiological' frequencies or on reflex sympathetic activation, a prompt and intense intestinal inhibition occurred regularly on distension of another, isolated part of the intestine, even when the splanchnic nerves had been cut. The rapidity of the onset of this intestino-intestinal in-

hibitory reflex had all the characteristics of a direct neurogenic mechanism, and it was first abolished when the nerve ramifications along the mesenteric vessels were destroyed. This purely local reflex does not appear to be influenced by any centrally controlled sympathetic nerve fibres.

It thus seems that, under normal circumstances, centrally induced inhibition of intestinal motility is practically exclusively dependent on the hormonal component of the sympatho-adrenal system.

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